Title

TPX-100 leads to marked, sustained improvements in subjects with knee osteoarthritis: pre-clinical rationale and results of a controlled clinical trial

Authors

McGuire, D
Lane, N
Segal, N
et al.

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SLEEP INTERVENTIONS FOR OSTEOARTHRITIS AND SPINAL PAIN: A SYSTEMATIC REVIEW OF RANDOMIZED CONTROL TRIALS

P.H. Ferreira †, K.K. Ho †, M.B. Pinheiro †, D. Aquino Silva ‡, C. Miller §, R. Grunstein §, M. Simic †. † *Univ. of Sydney, Sydney, Australia;* ‡ *Univ.e Federal de Minas Gerais, Belo Horizonte, Brazil;* § *CIRUS, Sydney, Australia*

Purpose: To determine if sleep interventions improve pain and sleep in people with osteoarthritis and/or spinal pain.
Methods: An electronic database search was conducted in Medline, Embase, AMED, PsycINFO, CENTRAL, CINAHL and PEDro from their inception date to April 2016. Keywords relating to "sleep", "osteoarthritis", "spinal pain", and "randomized control trial" were combined. Eligible studies were randomized control trials (RCT) from peer reviewed journals which investigated the use of sleep interventions for people with osteoarthritis and/or spinal pain. Sleep interventions were defined as interventions which aim to directly improve sleep related outcomes, including both non-pharmacological and pharmacological methods. Two investigators independently screened the literature search (title and abstract, followed by full text), extracted data and assessed methodological quality of included studies. Meta-analyses were performed to pool effect sizes for pain and sleep quality. Sensitivity analyses were performed with the following criteria: osteoarthritis or spinal pain, any sleep intervention, compared to a control/placebo group, ≥10 participants per group and PEDro Score≥6/10. The review protocol was registered with the International Prospective Register of Systematic Reviews (CRD42016036315).
Results: Of 1199 unique records, 97 underwent full text screening and 22 studies were included. 14 studies examined spinal pain, six for osteoarthritis, and two were mixed. Sleep interventions were cognitive behavioural therapy (CBT) (n = 8), pillows (n = 4), sleep medication (n = 3), exercise (n = 2), massage (n = 2), music (n = 1), acupuncture (n = 1), and mattresses (n = 1). Intervention periods ranged from four to ten weeks. Seven studies combined sleep and pain interventions, however none combined CBT for sleep with exercise or physiotherapy. Overall pooled post-treatment results (mean age = 33-73 years, n = 1339) had high heterogeneity scores ranging from 62-95%. Random effects estimates showed that sleep interventions led to significant improvements in pain (standardized mean difference 4.94, 95% confidence interval [1.47-8.42], $P = 0.005$) and sleep quality (9.13, [4.36-13.90], $P<0.001$). After sensitivity analyses, 7 RCTs were incorporated into the meta-analysis (mean age = 42 to 72 years, n = 354), with heterogeneity scores ranging from 10-45%. The pooled fixed effect estimates showed significant improvements in pain (10.78, [6.84-14.72]; $P<0.001$) and sleep quality (8.21, [4.83-11.58]; $P<0.001$).
Conclusions: Sleep interventions alone are likely to improve pain and sleep quality for people with osteoarthritis and/or spinal pain. Although the magnitude of change may not be clinically significant, further high-quality studies using CBT for sleep in conjunction with other interventions for people with osteoarthritis and/or spinal pain should be conducted.

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TPX-100 LEADS TO MARKED, SUSTAINED IMPROVEMENTS IN SUBJECTS WITH KNEE OSTEOARTHRITIS: PRE-CLINICAL RATIONALE AND RESULTS OF A CONTROLLED CLINICAL TRIAL

D. McGuire †, N. Lane ‡, N. Segal §, S. Metyas ‖, H. Barthel ¶, M. Miller †, D. Rosen †, Y. Kumagai †. † *OrthoTrophix, Oakland, CA, USA;* ‡ *Univ. of California, Davis, Sacramento, CA, USA;* § *Kansas Univ. Clinical Res. Ctr., Kansas City, KS, USA;* ‖ *Covina Arthritis Ctr., Covina, CA, USA;* ¶ *Barthel Clinic, Santa Barbara, CA, USA*

Purpose: TPX-100 is a 23-amino acid peptide derived from Matrix Extracellular Phosphoglycoprotein (MEPE), a Small Integrin-Binding Ligand, N-linked Glycoprotein (SIBLING) family protein. TPX-100 has been shown to induce articular cartilage proliferation in goats (N = 8/dose group) after a standardized full-thickness chondral defect and treatment with 4 weekly intra-articular (IA) injections of TPX-100 vs. vehicle (25, 125 or 250 mg/injection). After 6 months, histopathological staining in TPX-100-treated joints indicated robust articular (hyaline) cartilage formation. Additionally, IA TPX-100 reduced joint damage and improved osteoarthritis scores vs. vehicle in rats after standardized ACL transection and partial medial meniscectomy. This Phase 2 study evaluated safety, tolerability and preliminary efficacy of TPX-100 by IA administration in subjects with bilateral patellofemoral osteoarthritis (PFOA). Each subject served as his/her own control, intended to minimize effects of age, sex, genetic factors, and activity levels on outcome measures.
Methods: Subjects with ICRS grade 2-3 PFOA, confirmed by centrally-read screening MRI, were enrolled at 15 sites. One knee was randomly assigned to receive 4 weekly injections of TPX-100, while the contralateral knee received placebo injections. Investigator, subject, site and sponsor were blinded to treatment assignment. In Part A of the study, 4 dose cohorts (n = 6–9 subjects/cohort) received 20, 50, 100 or 200 mg/injection. Safety/tolerability of each cohort was evaluated by a Safety Review Committee (SRC). In Part B, all subjects received 200 mg/injection. Quantitative MRIs, obtained at baseline, 6 and 12 months, were read centrally. Validated patient-reported outcomes (PROs) included the Knee Osteoarthritis Outcome Score (KOOS), appropriate for younger, more athletic subjects, and the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC).
Results: All subjects who received 4 weekly 200 mg injections, with at least one follow-up MRI, were analyzed (n = 93 subjects, 186 knees). The study population was typical of the knee OA population in the U.S. (median age, 58.4 years; BMI 30.3), and 68 of 93 subjects (73%) also had ICRS grade 2 − 4 mild to severe bilateral tibio-femoral osteoarthritis (TFOA). Safety: There were no drug-related SAEs and no dose-limiting toxicities across doses. Common adverse events such as knee pain had virtually identical incidences in control and TPX-100-treated knees. Efficacy: Only 14% of knees changed in cartilage thickness/volume over the 12 months of the study. Quantitative MRI revealed no measurable between-knee structural differences in this small sample. However, statistically significant ($P<0.05$) and clinically meaningful differences in KOOS and WOMAC scores were demonstrated compared with placebo-exposed knees at 6 or 12 months or both, including activities of daily living, sports activities, and knee-related quality of life. Comparing TPX-100 treated knees vs. control knees, at 12 months; there was a significant difference in pain ascending and descending stairs, a chief complaint in PFOA. Overall, use of analgesics, including non-steroidal anti-inflammatory medications, declined markedly (62.5%) during the study.
Conclusions: TPX-100, administered in 4 weekly intra-articular injections (200 mg/injection), is safe, well tolerated, and associated with statistically significant and clinically meaningful functional benefits sustained to at least 12 months. Improvement in knee functional status with reduction in disease burden represents a key therapeutic goal in OA therapeutic development. The small sample size of knees with MRI changes in cartilage thickness/volume limited the power of this study to detect differences between knees in these measures. However, pre-clinical large and small animal data indicate the structure-modifying potential of TPX-100, which may be demonstrated with a longer study involving a larger sample size.

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SELF-REPORTED HOME EXERCISE ADHERENCE – FACT OR FICTION? A VALIDITY AND RELIABILITY STUDY USING CONCEALED ACCELEROMETRY AMONG PEOPLE WITH KNEE OSTEOARTHRITIS

P.J. Nicolson †, R.S. Hinman †, T.V. Wrigley †, P.W. Stratford ‡, K.L. Bennell †. † *Univ. of Melbourne, Melbourne, Australia;* ‡ *McMaster Univ., Hamilton, ON, Canada*

Purpose: The benefits of exercise for older adults with knee osteoarthritis (OA) are undisputed. Given the chronic nature of OA, home exercise programs provide an economic and sustainable intervention option. However, for these programs to be beneficial, patient adherence is crucial. Self-reported adherence measures such as exercise diaries and simple self-rated scales are commonly used both clinically and in research, yet it has been acknowledged that these measures are vulnerable to reporting bias, particular over increasing periods of recall, and little evidence exists demonstrating their validity or reliability. The objectives of this study were threefold: (i) to examine concurrent validity of adherence over 12 weeks measured via an exercise diary compared to adherence simultaneously measured using a concealed accelerometer in a cuff weight, among a cohort of older adults with chronic knee pain undertaking a home strengthening program; (ii) to examine the validity of a self-rated adherence scale with increasing duration of recall from 2-12 weeks compared to accelerometer measured adherence; and (iii) to evaluate test-retest reliability of the self-rated adherence scale.